Pharmacodynamics

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Two-state model of drug-receptor interaction

- Full agonists shift equilibrium “fully” towards the active conformation

Ra

في المحاضرات اللي قبل ، كنا نفترض انه الreceptor بدون ما يشبك فيه ligand يكون inactive حتى كنا نحطه بالأحمر إذا بتتذكروا، و إذا شبك فيه ligand بصير اخضر active
لكن اجت نظرية أخرى و اثبتت لنا انه ال receptor لحاله ممكن يكون ب 2 states :
1.inactive-nonfunctional/ Ri -
2.active form /Ra حتى لو مش شابك فيه اشي
اسم النظرية : two-state model theory

- Partial agonists shift equilibrium “partially” towards the active conformation

Ra

- Sub-maximal effect with receptors completely occupied

a full agonist will have a higher affinity for the receptor while a partial agonist will have less of that affinity. We also said that the full agonist will induce more of the drug receptor coupling for it to give me a response while a partial agonist will have less effect on that coupling process.

تذكّر :

what is the difference between a full agonist and a partial agonist?
We have differences among the drugs in their physical and chemical characteristics that make this distinction.

تشبيه الفكرة بالكرسي ، الصفحة القادمة

ملخص كلام الدكتورة بالعربي

نفترض في شخص بده يعطي المحاضرة ـــهذا هو ال receptor
و الكرسي الذي يجلس عليه ـــهو ال agonist

الشخص بإمكانه إعطاء المحاضرة بدون جلوس على الكرسي ، بس هذا سيصرف من طاقته
إذا جلس على الكرسي (full agonist) رح يعطي المحاضرة بدون ما يصرف طاقة يعني
و هو مرتاح ، يعني بحب يضل زي هيك مدة طويلة
الpartial agonist زي كإنه كرسي لكنه مش كثير مريح ، لذلك سيصرف
الشخص(receptor) طاقة اقل من لما يكون واقف تماما، لكن الشخص لا يفضل المكوث
بهذه الحالة مدة طويلة

كلام الدكتورة الحرفي ... مهم

Let's say I am the receptor and I need to work on making this lecture here today. Now let's say I do not have a chair at all. But in order for me to give the lecture, I have to sit in a way that I can access my computer. Now sitting in that way without a chair and bending to be at the same level of the computer will allow me some access for that computer. So I will be able to produce my function which is giving the lecture to some extent. But because I'm just sitting there bending in an uncomfortable position, I have to use more energy to stay in that position and be able to produce my effect which is giving the lecture. Now let's say I have that comfortable chair in my office now and I sit at that comfortable chair. Now I'm at the same level of my computer. I'm sitting relaxed and I'm able to use my computer and give my product which is the lecture. In this case, I need to consume less energy to stay in that position and give the lecture. And this applies the same for the drug and the receptor. So if I have the receptor in the RA form without the presence of drug bound to it or an agonist bound to it, it will still give me some effect. It will stay for some time in that active form but it's utilizing much energy to stay in that form. That's why it keeps going back to standing up(or to theRi form) the unfunctional or the inactive form. But if I gave my receptor that comfortable fancy office chair, which is the full agonist, it's going to be able to stay in that active form for more time. So we're going to shift the equilibrium more towards that active form or the RA confirmation. So my agonist or my activator arug is actually the comfortable chair that lowers the thermodynamic energy that the receptor need to spend in order for it to stay in the active form orRA confirmation. That's why we say a full agonist will shift the equilibrium fully towards the active confirmation. Now what about a partial agonist?
The partial agonist is a not very comfortable chair. So if I bring a regular wooden chair and I sit on it now I am consuming less energy to stay in that position where I can access the computer.
But this chair is kind of rigid. It's not very comfortable. So I will not stay in that position long enough as I would if I have a comfortable chair. So the partial agonist will shift the equilibrium partially towards the active confirmation because I would spend some energy to stay in that confirmation more than that if I did not have a drug or an agonist but less than that if I have a very comfortable chair.

Two-state model of drug-receptor interaction

- The receptor is postulated to exist in the inactive, nonfunctional form (Ri) and in the activated form (Ra).
-
- Thermodynamic considerations indicate that even in the absence of any agonist, some of the receptor pool must exist in the Ra form some of the time and may produce the same physiologic effect as agonist-induced activity.
- Agonists have a much higher affinity for the Ra configuration and stabilize it, so that a large percentage of the total pool resides in the Ra–D fraction and a large effect is produced

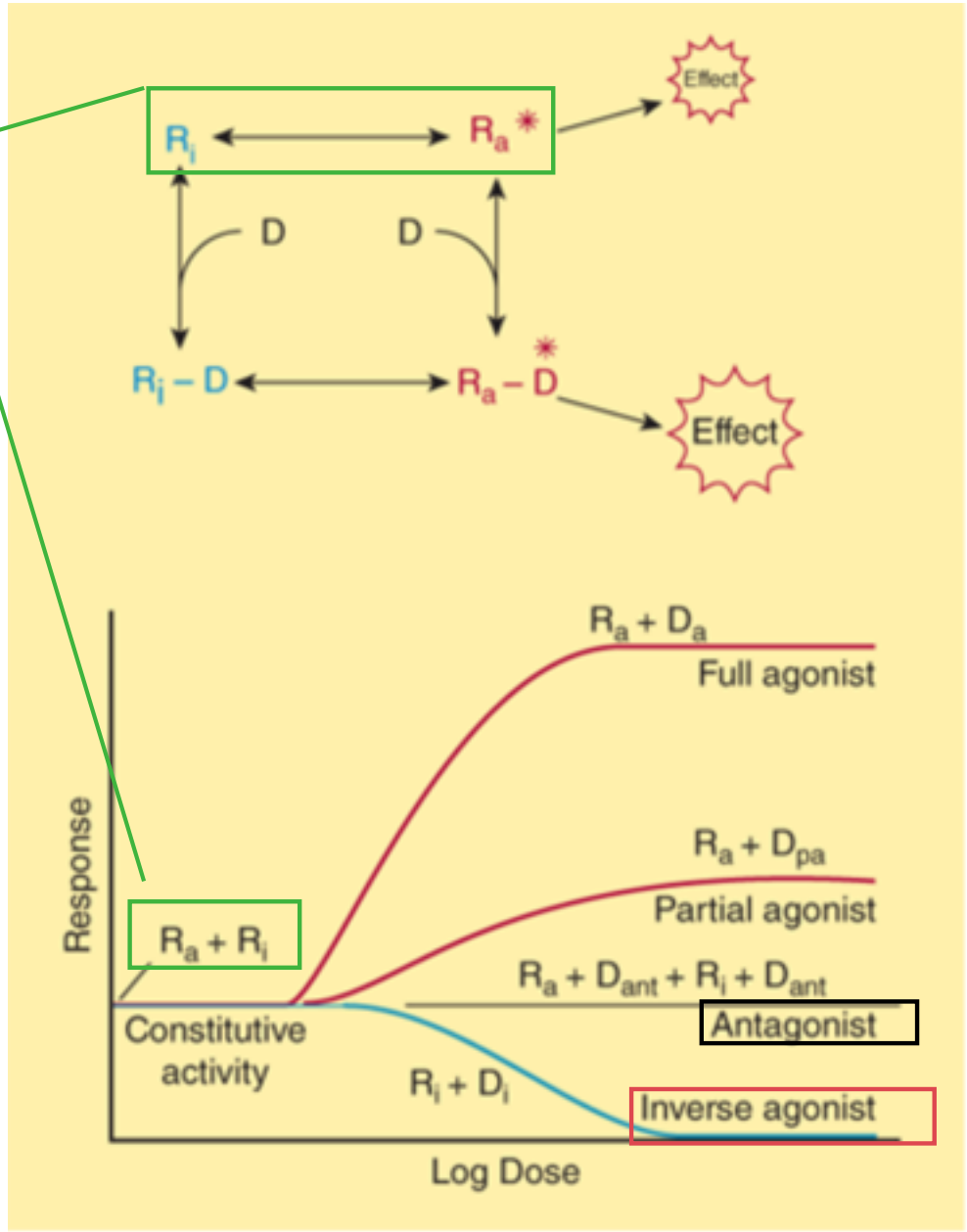
Constitutive Activity

شرحت الصفحتين القادمات قبل هذه

- The effect of receptors, occurring in the absence of agonist, is termed constitutive activity.
- The recognition of constitutive activity may depend on the receptor density, the concentration of coupling molecules (if a coupled system), and the number of effectors in the system.

شرح مني الفهم ...
في عندي خلية ، عليها receptor بس ما في عليها agonists ، رح ضفت عليها antagonist شو رح يكون الاثر ؟؟؟ ولاا اشي يعني ال antagonist ما اله اثر بدون agonist — لكن ال inverse agonist مستعد يشتغل بأثر عكسي لوحده حتى لو ما في agonist

لاحظوا كيف عندي الحالتين ، رغم انه ما في drug شابك



A neutral antagonist is a drug that will bind to the receptor and will prevent the binding of an agonist to it.So it will NOT cause a shift in that equilibrium. It will just hinder the binding of any other agonist to that receptor.

inverse agonist: It is an antagonist but it is a drug that shifted the equilibrium more towards the inactive confirmation.

Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology, 13th Ed.
www.accesspharmacy.com

Inverse agonists:

While antagonists are traditionally thought to have no functional effect in the absence of an agonist, some antagonists exhibit “inverse agonist” activity because they also reduce receptor activity below basal levels observed in the absence of any agonist at all.

عشان هيك سميته agonist و ليس antagonist

لا تنسوا أنه الـ antagonist ما بعمل اشي ، هو فقط بمنع ال agonist إنها تشبك ، لكن ال inverse agonist نفسه لما يشبك على الreceptor بعمل اثر
يعني هو نفسه بشتغل على الreceptor اله اثر شخصي (مش زي الantagonist الذي لا يملك اثر فقط يعمل على منع الagonist)

عشان هيك سميته inverse

كلام الدكتورة الحرفي

inverse agonist is a drug that will bind to the receptor and change the equilibrium more towards the inactive confirmation. So why did we
call it an agonist? Because it is a drug that's bound to the receptor and it caused a shift in the equilibrium. So it caused an effect and this is different than what we learned about antagonist because we said antagonist do not have an effect. The net effect of them is zero. But the inverse agonist will do some effect. But this effect is opposite.
So we can say the effect is in the minus. So an inverse agonist is actually an antagonist that will reduce the receptor basal activity

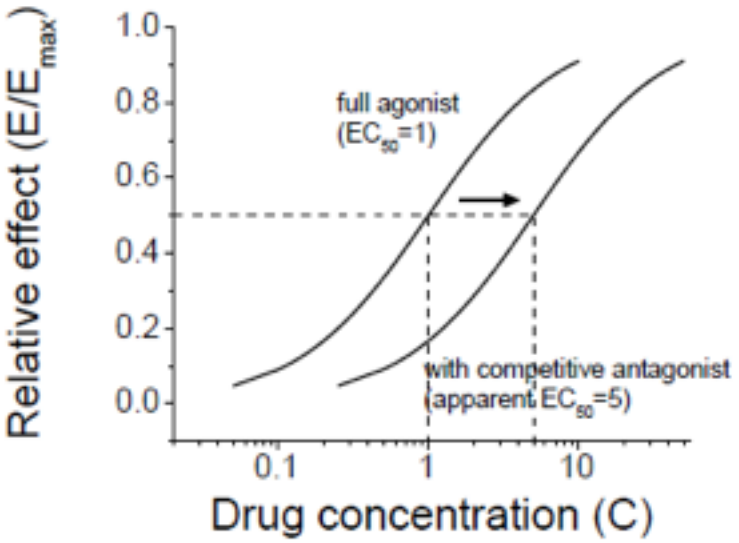
Competitive & Irreversible Antagonists

- Receptor antagonists bind to receptors but do not activate them
- The primary action of antagonists is to reduce the effects of agonists (other drugs or endogenous regulatory molecules) that normally activate receptors.

Competitive antagonists

- Bind agonist site
- Do not shift equilibrium towards active or inactive conformation
- “Neutral” antagonists

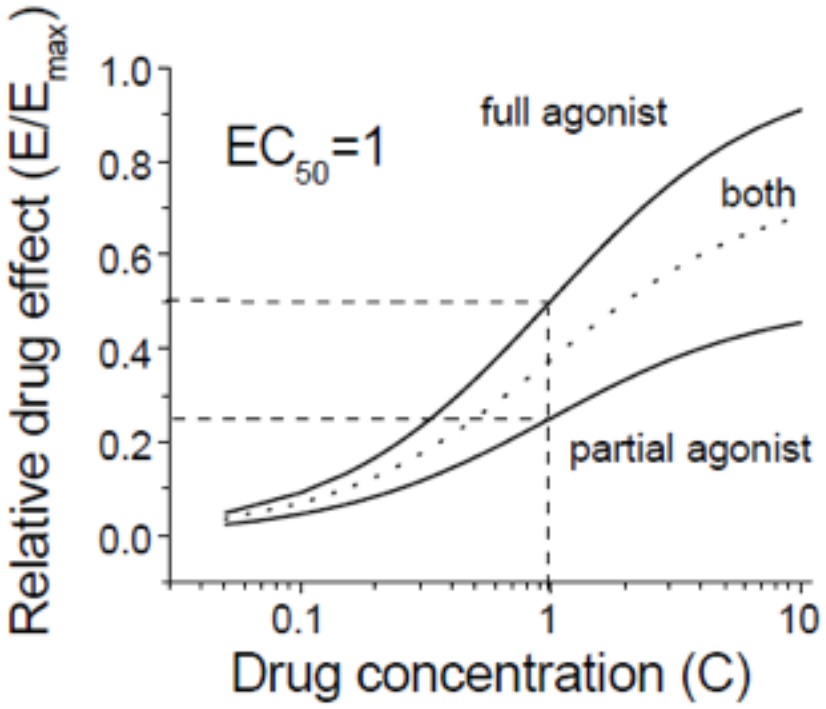
Right but parallel shift



partial agonist will bind to and activate the receptor but it's not able to elicit the maximum possible response that is produced by a full agonist.

in the presence of a full agonist the partial agonist will act as an antagonist because it's compete With the agonist for the same receptor and thereby it will reduce the ability of the full agonist to produce a maximum effect.so we wouldn’t see the Emax

مثال واقعي على الفكرة



We have an example actually for a drug that's used to help patients quit smoking.
The name of the drug is verinesilen or it has a commercial name called shantix . So Shantix is actually a partial agonist for the nicotinic receptor.
It is a medication that's used to treat nicotine addiction. It does so, by competing with the full agonist which is nicotine and reducing the maximum effect that nicotine would produce in the body which is decrease in the craving and the pleasurable effects that cigarettes or nicotine would give for a particular patient.So this partial agonist will bind to the nicotinic receptor (and if you remember in physiology the nicotine receptor is the acetylcholine receptor and it will prevent the nicotine (that's ingested by the cigarette by that patient) from receiving the full effect. Thus it will cause a decrease in the full effect of pleasure and craving that that patient is getting and by that we will start to desensitize the patient for nicotine.

Receptor Regulation

Next slide

A • **Sensitization or Up-regulation**

1. Prolonged/continuous use of receptor blocker
2. Inhibition of synthesis or release of hormone/ neurotransmitter - Denervation

B • **Desensitization or Down-regulation**

1. Prolonged/continuous use of agonist
2. Inhibition of degradation or uptake of agonist

Homologous vs. Heterologous

Uncoupling vs. Decreased Numbers

مثلاً عنا مريض قلب ، يأخذ beta blockers لمدة طويلة ،الجسم دائما بده ال homeostasis ، الجسم عنده degree of receptors و بده يحافظ عليهم ، ف أنا لما أعطي blocker لهذا ال receptor أنا عم بخالف ال homeostasis و هاد ما برضي الجسم ، ف بروح الجسم برفع عدد الreceptors عشان يعوّض اللي أنا منعته منهم ، فبصير عندي اتزان ما بين منعي لإلهم و اعادة تصنيع الجسم لإلهم و الأمور تمام ⚠️⚠️⚠️لكن إذا قرر المريض من كيفه انه يوقف أدويته (اللي هي beta blocker) رح يضطرب الاتزان : حيث انه قل ال blocking لانه راح الدواء و بنفس الوقت الجسم بعده عم بصنّع receptors كمان و كمان ، يعني كمية receptors هائلة لاستقبال ال adrenaline (endogenous ligand) !!! و تذكروا حكينا زمان انه دائما أنا عندي كمية من ال ligand اكثر من قدرة المستقبلات ، فالنتيجة ال Phisyological انه ممكن يصير عندي arrthmia , irregular heart rate وهذه مشكلة ال sudden stopping of medication كمان شيء ممكن يصير : انه مش بس ال receptors بصير الها unregulation ، بل حتى ال second messenger ممكن يصيرلي upregulation يعني كل ال transduction system inside the cell ف بالتالي تزيد ال sensitisation

A

مثلاً ال morphine-pain killer يعتبر opioid receptor agonist بنلاحظ انه لما نعطيه للمريض لمدة طويلة يصير عندي de-sensitisation يعني أنا محتاجة أعطيه جرعة اكبر عشان يستفيد ، ليش صار هيك ؟؟ لانه الجسم عمل downregulation للreceptors يعني قبل عددهم ، يعني الجسم يلاحظ اني أنا كثير قاعد بقعّل ال system ف أنا مش محتاجة كل هاد ، ف بروح بقلل الreceptors , طيب هل الحل اني اضل ارفع الجرعة للمريض ؟؟ لأ طبعًا لانه ممكن اوصل ال toxicity او أوصل ال plateau يعني الEmax

الحلول :

بقدر ارفع ال receptorsبالجسم by giving certain periods of weaning يعني بعطيه الدواء لفترة معينة بعدين برجع بقطعه مثلاً بعطيه اياه ١٢ ساعة بعدين بقطعه ، ف الجسم ما رح يحس انه في continuous activation ف ما رح يعمل down regulation

او الحل الثاني انه انقل لدواء يعمل بطريقة مختلفة

B

Variation in drug responses

&

Drug-Drug Interactions

Properties of an Ideal Drug

Effective E max عالية

Safety Therapeutic index عالي

Selective That means to be able to activate or inhibit a subset of receptor in a particular tissue without messing up with the function of receptors in tissues that we don't want to affect or target. And this helps us minimize the side effects of these agents or drugs.

Reversible Action the function need to be reversible uh because we don't want the effect of the drug to stay infinitely in the body

Predictable it's good to know the side effects ahead of time.

Freedom from drug interactions

Low cost

Chemically stable In GI does not need to disintegrate before it reaches its target. also in the shelf in the pharmacy. We don't want the drug to lose its active components before we start using it.

Sources of Variability in Therapeutic Responses

Similar drugs usually produce similar qualities of responses in patients, but might produce different intensities and duration of effects.

- **Dose, Dosage schedule, and Route of administration.**
- **Diurnal variation "Chronopharmacology".**
- **Age and sex of the patient.**
- **Drug reactions.**
- **Drug interactions: other drugs, diet, and environment.**
- **Placebo effect.**
- **Intercurrent illnesses.**
- **Tolerance.**
- **Genetic or racial factors, "Pharmacogenetics".**

Causes of Variability in Drug Response

Those related to the biological system

1. Body weight and size
2. Age and Sex
3. Genetics - pharmacogenetics
4. Condition of health
5. Placebo effect

ال DNA مسؤال عن تصنيع الإنزيمات المسؤلة عن metabolism of the dru و ال receptors..

مثلاً عندي مريض عنده مشاكل بالكلى ، حيث هي مكان ال excretion of the drug ف أنا بدي أشوف كم ضل عنده كفاءة بعمل الكلية بحيث يكون قادر على العمل على دوائي ، how much functionality still لانه ما بدي الدواء يتراكم عندي بدي يصيرله execration

ممكن المريض يشعر بتحسن بس لانه شاف انه أخذ دواء (يعين نفسيا بطيب) يعني هذا مو اثر الدواء الحقيقي ف أنا بروح يجيب مجموعتين من الناس ، جزء بعطيهم دواء عنجد ، و جزء بعطيهم حبّة (هي فعليا مو دواء - blacebo tablet) بس ما بنحكيلهم طبعًا — blinded study بحكي للجميع انه هذا الدوا رح يخفف الألم عندكم

في عندنا Double blinded study : هي انه اللي بعطي الدواء ما بعرف مين منهم actual و مين منهم placebo ولا المريض بعرف — بس في النهاية لما اجمع النتائج بعرف مين هيك و مين هيك

Causes of Variability in Drug Response

- **Those related to the conditions of administration**

1. Dose, formulation, route of administration.
2. Resulting from repeated administration of drug:
   drug resistance; drug tolerance-tachyphylaxis; drug allergy
3. Drug interactions:

   chemical or physical;
   GI absorption;
   protein binding/distribution;
   metabolism (stimulation/inhibition);
   excretion (pH/transport processes);
   receptor (potentiation/antagonism);
   changes in pH or electrolytes.

Pharmacogenomics:

The relation between the individual's genetic makeup to his/her response to specific drugs (entire genome).

Pharmacogenetics:

Interindividual variation in drug response that is due to genetic influences (specific gene).

Metabolism

- The liver is the major side of metabolism for many drugs, but other organs, such as lungs and kidney can also metabolize drugs.

- Many lipid soluble drugs are not readily eliminated from the body and must be conjugated or metabolized to compounds that are more polar and less lipid soluble before being excreted.

- Metabolism often, but not always, results in inactivation of the compounds.

- Some drugs are activated by metabolism, these substances called prodrugs.

Phase I metabolism

- Drug metabolism occur in two phases:
- Phase I reactions function (e.g., oxidation, reduction, hydrolysis) alter chemical reactivity and increase water solubility.
- Phase I reaction frequently catalysis by the cytochrome P450 system (also called microsomal mixed function oxidase).

$$\text{Drug} + O_2 + \text{NADPH} + H^+ \rightarrow \text{Drug}_{\text{modified}} + H_2O + \text{NADP}^+$$

they're responsible to metabolize most of the drugs that the patients receive.

- To date, 12 unique isoforms of this enzymatic system (CYP 2D6, CYP3A4) have been identified to play a role in human drug metabolism.

Polymorphism:
أشكال متعددة لنفس الجين
فبالتالي function مختلفة لنفس الجين

If mutation happen to more than 1% of population it is called polymorphism

هذا الاختلاف وال polymorphism
بال p450 أدّت إلى ٤ أشكال من الناس

Phase II metabolism

- If the metabolite from phase I is polar enough it will excreted by the kidney, But if it is still lipophilic to be retained in the kidney, a subequence Phase II metabolism will take place.

- Phase II consist of conjugation reaction with endogenous substances, such as, glucuronic acid, sulfuric acid, or an amino acid.

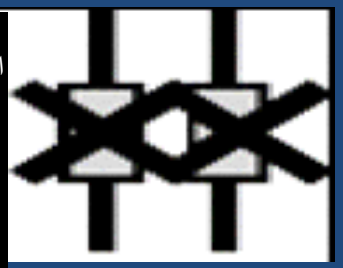
- Results in polar and usually more water soluble compounds.

Phenotypes of CYP450

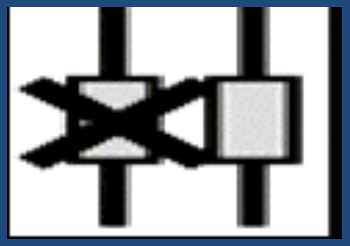
Isoforms of p450

1. Poor metabolizer (PM)
- has low metabolic capacity
- has two mutant alleles

إذا أعطيت warfarin لأربع مرضى
اول اشي ال PM رح يتراكم عنده الدواء بالدم لانه مش عم بتكسر
ف بالتالي رح يزيد ميوعة الدم لذلك bleeding time اطول
اما بالنسبة ل IM and EM هدول طبيعين رح يتصرفوا زي ما افترضت الدواء انه يعمل
لكن UM الدواء بسرعة تكسّر و راح ف رح يبطل يعمل ميوعة للدم فبالعكس رح يصير عندي thrombic event

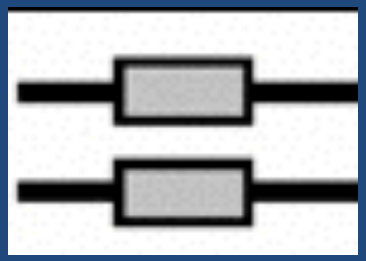


2. Intermediate metabolizer (IM)
- has metabolic capacity between PM and EM
-has one reduced activity allele and one null

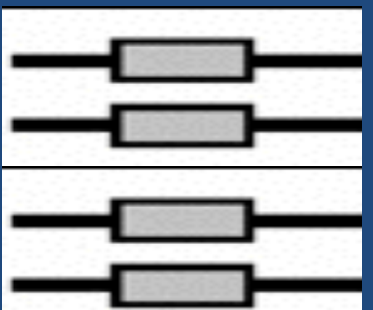


3. Extensive metabolizer (EM)
- has regular metabolic capacity
- has at least one and no more than two normal functioning alleles

لذلك أنا لازم اكون عارفة مريضي اي نوع ، هل معقول ادرس جينات كل مرضاي؟؟ لا طبعا لانه شوي مكلف ، لذلك الحل بركّز على الأدوية اللي الها severe consequences ساعتها لازم اعرف شو طبيعة المريض ، بالنسبة لل warfarin ما بنعمل هيك ، إنما بنقيس ال prothrombin time يعني of the patient clotting time



4. Ultrarapid metabolizer (UM)
- has higher metabolic capacity than EM
- has multiple copies of functional alleles



هذا السلايد تم شرحه بمحاضرة سابقة

Cytochrome P450 system

- Cytochrome P450 system dependent enzymes are important target for drug interaction because they can be induced or inhibited by certain drugs.

rifampen is an antibiotic used for the treatment of tuberculosis. It is a cytochrome P450 inducer.

- Cytochrome enzymes Inducers like rifampin and carbamazepine are capable of increasing the synthesis of one or more of isoforms. For example, Rifampin significantly decreases the plasma concentration of HIV protease inhibitors.

inhibitor of cytochrome P450.

- Cytochrome enzymes inhibitors, Omeprazole inhibits three CYP isoforms that are responsible for warfarin metabolism, leading in an elevation in the warfarin concentration, and so greater inhibition of coagulation, leading in to more risk of serious bleeding reaction,

Drug-drug interaction

ال drug drug interactions ما بتصير على ال p450 فقط إنما بتصير في أماكن مختلفة ايضًا دواء يوثر على الآخر و (يزيد او يقلل اثره)

- When two drugs taken together, there is a possibility that the drugs will interact with each other to cause unanticipated effect. Usually increase or decrease in the desired therapeutic effect.

- Drug-drug interaction can occur in the following sites

1. at the side of absorption, tetracycline is not absorbed from the GI tract if calcium product present in the stomach. إذا أعطيت ال tetracycline (مضاد حيوي) مع منتجات الألبان (calcium) رح يصير تفاعل رح يترسب بالمعدة و لا يمتص ، عشان هيك بننصح المرضى ما ياخدوا ال antibiotic مع مشتقات الألبان او اي دواء آخر يحمل ال كالسيوم مثل الأدوية التي تخفف من حموضة المعدة
2. during biotransformation (CYP 450).
3. At the site of action, drug antagonism.

Drug-drug interaction

3. During excretion, digoxin (For heart failure) and quinidine (For arrhythmias) are both excreted from the same sites in the kidney. The quinidine will be excreted first because it is more competitive for these sites, resulting in increased serum levels of digoxin.

الفكرة انه الدوائين هدول الهم نفس ال receptor بالkidney لكن الquinidine اله affinity
اعلى ف بالتالي يخرج اولاً — إذا سيتراكم ال digoxin ممكن يسبب مشاكل بالقلب

4. During distribution, aspirin competes with methotrexate (Chemotherapeutic agent) for protein binding sites, and because aspirin (Pain killer) is more competitive for the sites, resulting in increased release of methotrexate and so increase toxicity to tissues.

بتتذكروا لما حكينا انه في أدوية بتحب تشبك مع ال plasma proteins و
بالتالي تكون غير فعالة و هذا يمثل مخزن reservoir لهذا الدواء ؟؟ لو أعطيت
دوائين بحبوا يشبكوا على ال plasma protein نفسه مثل ال albumin —>
إذا شبك الaspirin رح يفكّ ال methotrexate الذي يعد toxic للدم لانه
drug interaction ، عشان هيك لازم ننتبه لهذا ال chemotherapeutic

Adverse effect

- Adverse effect are undesired effect that may be unpleasant or even dangerous they can occur for many reasons:

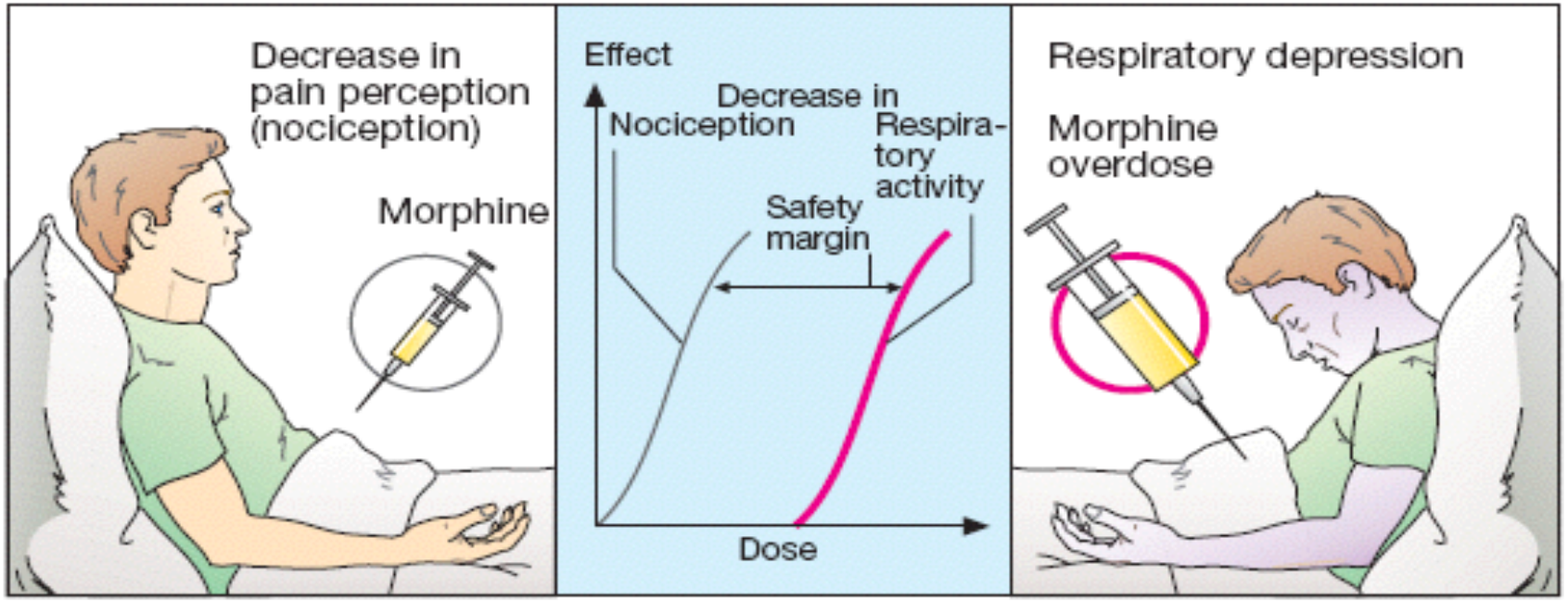
1. The drug may have other effects on the body besides the therapeutic effect.
2. The patient is sensitive to the drug. Allergic
3. The patient is taking too much or too little of the drug.

- the nurse, as the most frequently administers medications, must be constantly alert for sign of drug reactions of various types.

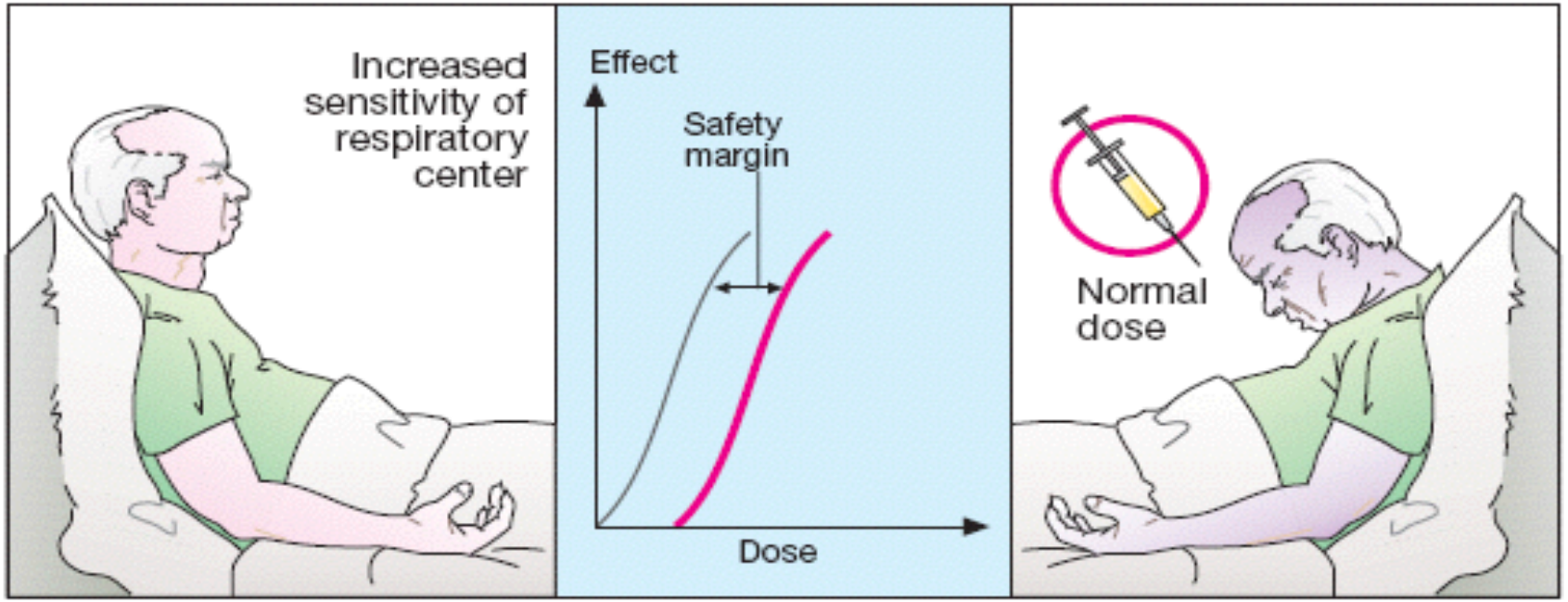
these adverse effects are noted by the nurse but they also should be noted by the physician or the health professional who administered that medication for the patient. So we need to be careful about any adverseeffect that are unpredictable and might arise for that patient.

Remember !!!

- With every drug use, unwanted effects must be taken into account.
- Before prescribing a drug, the physician should therefore assess the **risk: benefit ratio.** الطبيب لازم يقدّر هل النفع من هذا الدواء اكثر من الخطر ؟
- In this, knowledge of principal and adverse effects is a prerequisite.



A. Adverse drug effect: overdosing



B. Adverse drug effect: increased sensitivity

Adverse Drug Reaction

- Adverse drug reactions are classified as predictable or unpredictable.
- A predictable drug reaction is related to the pharmacological actions of the drug.
- An unpredictable reaction is related to immunological response (hypersensitivity reactions) or non-immunological response Age

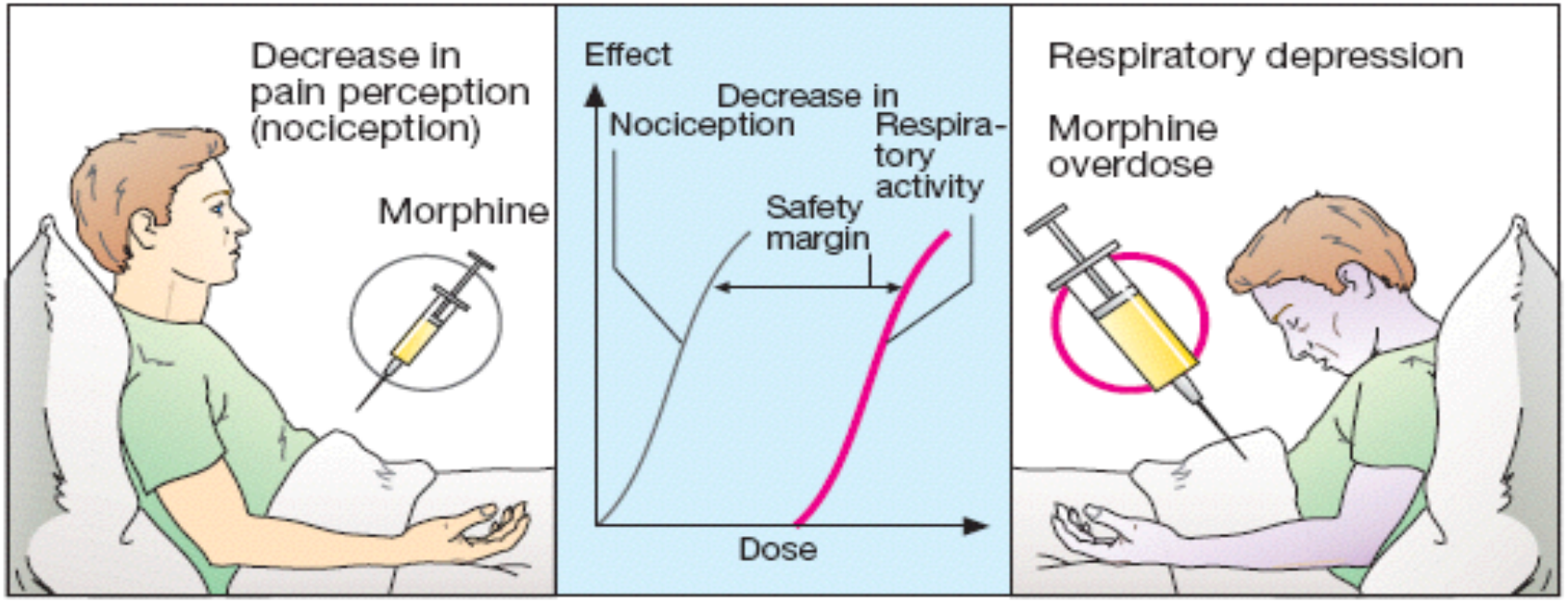
Effect of Age

we said one important variable that can cause this differences among the different individual is the age of the patient. So we have some drugs like morphine here. Morphine is a painkiller and it can decrease the pain perception in an individual.If we take too much of morphine will result in morphine overdose and this is usually resulted from respiratory depression. Now the same drug will have a different response in an older individual.

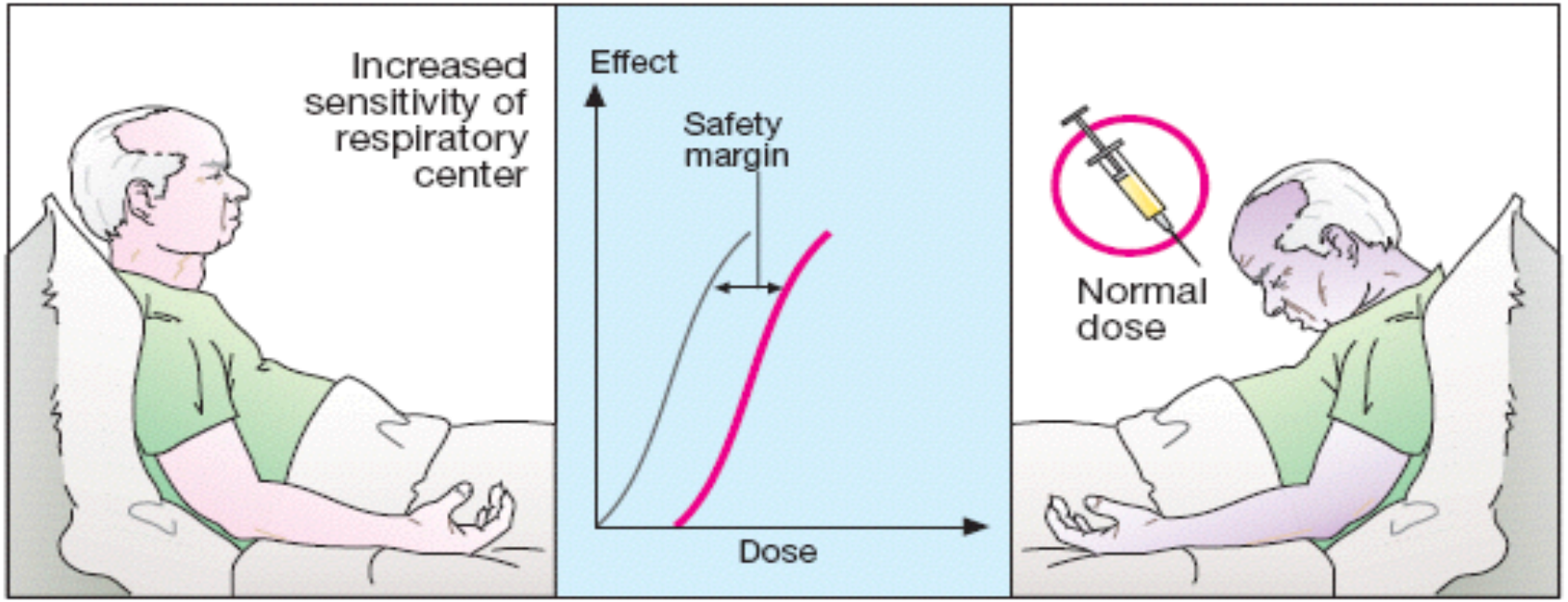
So in the lower half of this figure here we have an elderly patient who has been prescribed morphine. But we have to know ahead of time that ⚠️for an older patient we have increased sensitivity in the respiratory system.So the safety margin for an elderly patient is not the same as that for a young patient. ✅So what would be a normal dose for a young adult would be a

fatal dose for a elderly patient. So this is part actually of the adverse drug actions. We have to predict what these effects are going to be and what would these effects be in a different population geriatric population or also pediatric population.

كبار السن الأطفال

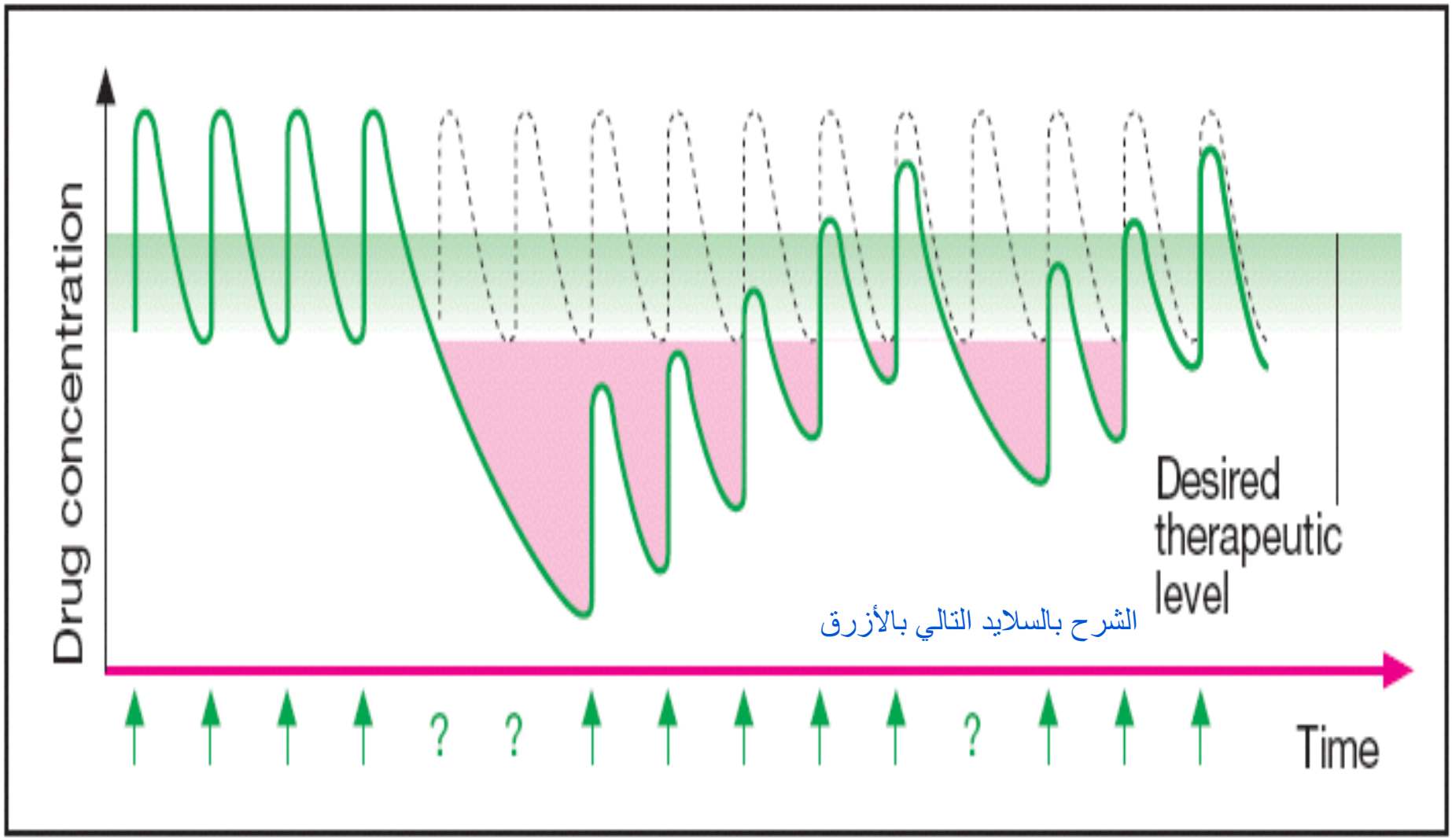


A. Adverse drug effect: overdosing



B. Adverse drug effect: increased sensitivity

Compliance مدى التزام المريض بتعليمات الطبيب



Time course of drug concentration with irregular intake

Adults >65 years old

- growing population

الحمد لله بسبب تطور health care system و ال drug discovery الناس صارت تعيش اكثر

لكن معظم المشاكل اللي بتصيرلهم بسبب الدواء مثل drug interactions او بسبب overdose

- 20% of hospitalizations for those >65 are due to medications they’re taking

لازم ناخد الدواء بأوقات معينة عشان نحافظ على ثبات مستواه بالجسم عشان نحصل الاثر المرغوب / minimum effective concentration, لما المريض ما ياخد الدواء رح ينزل التركيز عن ال MEC , لما يكون المريض بده ياخد ٣ حبات باليوم احتمالية انه ينسى عالية جدًا ، خصوصي كبار السن geriatric

if we give a lot of doses of the drug , the compliance of the patient

عشان هيك بنحاول نعمل ال دواء to have a long dosing interval يعني ينعطى الدواء حبة وحدة باليوم

Other factors affecting the elderly

Pharmacokinetics

- Decrease in total body water (due to decrease in muscle mass) and increase in total body fat affects volume of distribution
- Water soluble drugs: lithium, aminoglycosides, alcohol, digoxin
  - Serum levels may go up due to decreased volume of distribution
- Fat soluble: diazepam, thiopental, trazadone
  - Half life increased with increase in body fat

Accumulating

- Oxidative metabolism through cytochrome P450 system does decrease with aging, resulting in a decreased clearance of drugs

The dose that we give for an elderly patient who have not as well functioning liver enzyme is going to be lower than that for a patient who is young where the liver function is completely maintained.

Pharmacokinetics: Excretion and Elimination

- GFR generally declines with aging, but is extremely variable
  - 30% have little change
  - 30% have moderate decrease
  - 30% have severe decrease
- Serum creatinine is an unreliable marker
- If accuracy needed, do Cr Cl

we have to rely on the clearance of the medication rather than the serum level.

Example: Creatinine Clearance vs. Age

Age	Scr	CrCl
30	1.1	65
50	1.1	53
70	1.1	41
90	1.1	30

Clearance يقل مع العمر
مع انه ال plasma level is the same

Other factors affecting the elderly

Pharmacodynamics (PD)

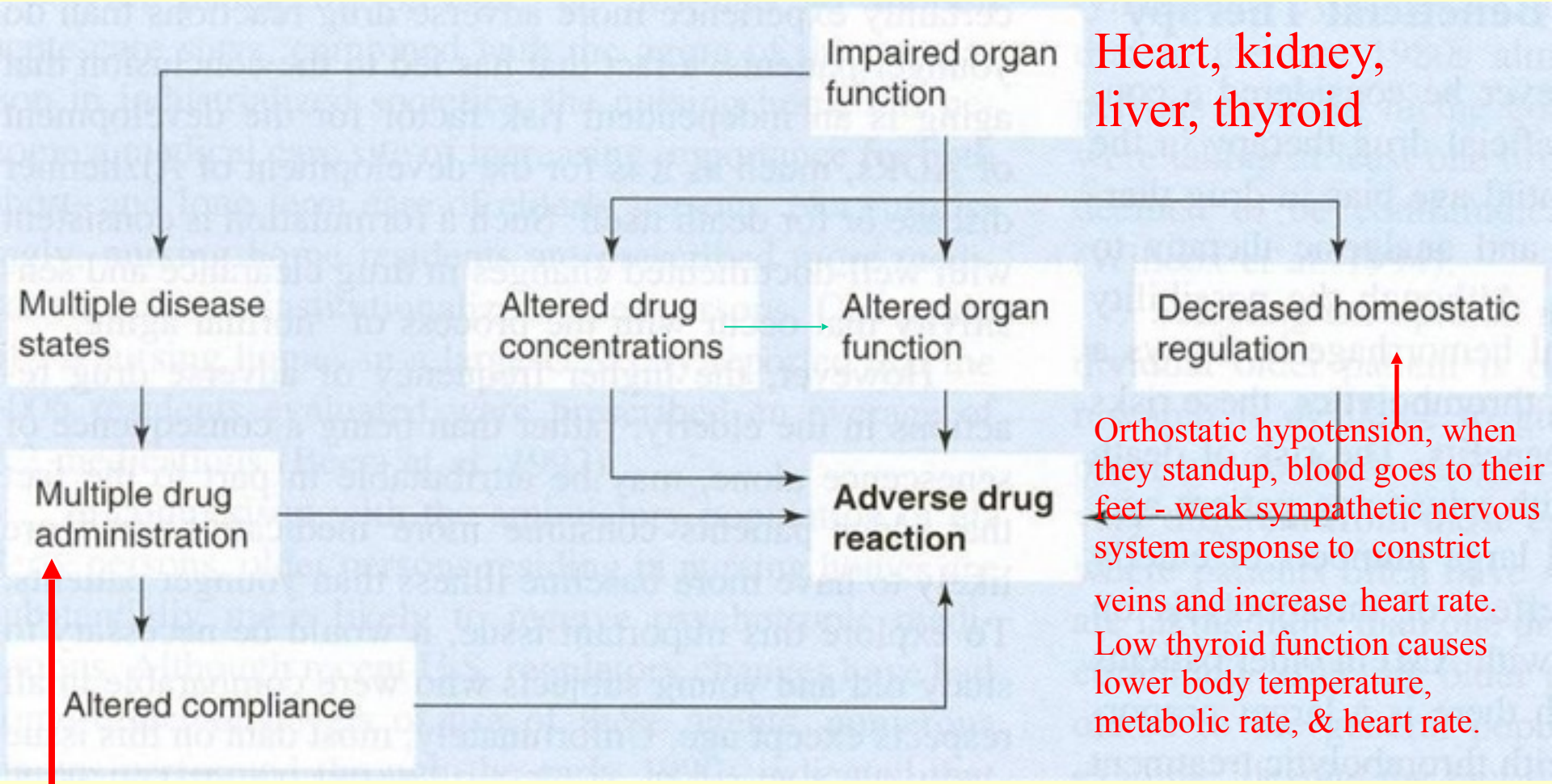
- Definition: the time course and intensity of pharmacologic effect of a drug
- Age-related changes:
  - ⇑ sensitivity to sedation and psychomotor impairment with benzodiazepines
  - ⇑ level and duration of pain relief with narcotic agents
  - ⇑ drowsiness and lateral sway with alcohol
  - ⇓ HR response to beta-blockers
  - ⇑ sensitivity to anti-cholinergic agents
  - ⇑ cardiac sensitivity to digoxin

I don't want you to remember all these examples but know that we will have differences in the intensity and time course of the pharmacological effect of drugs with age.

كل هذا حصل بسبب regulation اللي حصل لل receptors or single transduction pathway

Factors contributing to adverse drug reactions in elderly patients

كل الكلام بهذا السلايد مكتوب أصلا حتى اللي بالأحمر و الأزرق ، هذا الدكتورة كاتبتيه و قرأت كل الرسمة



Polypharmacy

How many prescription medications are too many? >4 or >6
Many elderly people receive 12 medications per day

Pediatric Patients

- Higher proportion of water
- Lower plasma protein levels
  - More available drug
- Immature liver/kidneys
  - Liver often metabolizes more slowly
  - Kidneys may excrete more slowly

Pediatric Dosing

Traditionally, for less frequently used drugs, extrapolation is done from adult dose on a weight or surface area basis

Problems

- Absorption may be more or less than adult
- Clearance of some drugs in children is affected by maturation, as well as size
  - Cytochrome P450 enzyme system matures over time
  - Glomerular filtration changes over time
- Drug targets may vary with age

CYP Enzymes

- CYP isoforms vary with age
- For example, clearance of midazolam by CYP 3A4 and 3A5 goes from 1.2 ml/min/kg to 9 ml/min/kg over first few months of life

- Carbamezapine (3A4) clearance faster in children than adults – requires higher doses

- “Children are not Small Adults”

❌❌❌يعني ما بنفع الام تحكي أنا وزني ٦٠ كجم و ابني ٣٠ كجم يعني هو قد النصف ، يعني إذا أنا باخد dose 500 بروح بطعميه 250

الأطفال الهم دراسات خاصة

اللهم أعزّ الإسلام والمسلمين ، وحّد صفهم و اجمع شملهم و ألف بينهم
اللهم في هذه الأيام المباركات لا تدع لنا ذنبا إلا غفرته ولا هما إلا فرجته ولا مريضا إلا شافيته ولا ميتا إلا رحمته
(ربنا اتنا في الدنيا حسنة و في الآخرة حسنة و قنا عذاب النار)